REMARKS

A. Claim Amendments.

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

Claims 32 and 34-35 are requested to be cancelled.

Claim 18 is currently being amended.

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

After amending the claims as set forth above, claims 18-19 and 23-24 are now pending in this application.

B. Response to Requirements Regarding Oath/ Declaration.

The Office Action objects to the Oath/ Declaration as including non-initialed changes. Applicants respectfully disagree—the portion of the document signed by inventor Christopher Scott which contains the handwritten changes includes his initials, "CS", next to the changes. Applicants therefore submit that the document is acceptable under 37 CFR § 1.52.

C. Response to Claim Objections and Ambiguity Rejection (§ 112, second paragraph) of Claim 23.

The objection to Claim 23 has been addressed by amendment to delete the second 'the' following –wherein--. Further, the phrase "the inhibitory activity" has now been amended to clarify the source of its antecedent basis in Claim 18.

D. Response to New Matter Rejections.

The written description rejections at pages 5-6 of the Office Action do not specifically identify the language of the claims believed to be new matter. As to Claims 18 and 23 and dependent claims 19 and 24, Applicant assumes that the rejection is directed to the phrase identifying "Domains I or II" as the locations of the mutations in the phospholamban molecule.

In this respect, the rejection has been rendered moot by the amendment of the claims to be directed to the S16E and K3ER14E mutants. However, Applicant notes for the record that the mutations to both of these molecules appear in Domain I of the phospholamban molecule, while the mutation in the disclosed V49A mutant (formerly the subject of Claim 34) occurs in Domain II of the molecule (see, page 3, lines 7-15 of the Specification describing the domain structure of phospholamban; and page 17, lines 10-20, describing point mutations that diminish SERCA2 inhibitory activity. Thus, the Specification clearly provided support for claim language drawn to phospholamban molecules having mutations in Domains I or II.

As to claims 32 and 34 (now cancelled in view of the changes made to Claim 18), the Office Action's statement that "mutations consisting of R14E, S16N, S16E or K3E/R14E or V49A" are not taught in the Specification is not understood. Each such molecule is described in the Specification at page 17, lines 10-20, and by sequence in the Sequence Listing. Although the rejection is moot as to Claims 32 and 34, Applicant confirms that the presently claimed S16E and K3E/R14E molecules are clearly described in the Specification. For example, the S16E mutant and its activity is described at page 17, lines 10-20; Example 5, page 29, lines 27-30; and in Sequence ID No. 13. The K3E/R14E molecule and its activity is described at various places throughout the Specification; e.g., page 17, lines 10-20; page 22, lines 5-25 (including Table 2), and in Sequence ID No. 6.

Applicants therefore respectfully suggest that the Specification provides clear written description for the molecules claimed, and that no new matter is added to the application by the

claim amendments. Reconsideration and withdrawal of the new matter rejections is therefore requested.

E. Response to Enablement Rejection of Claims 18-19, 23-24, 32 and 34-35.

Applicants understand the basis of the enablement rejection to be that, although expression of phospholamban mutants followed by a corresponding decrease in calcium transients in myocytes is demonstrated by data in the Specification, it has "failed to provide any guidance and/or working example that correlate to the treatment of a condition associated with cardiac muscle contractility or congestive heart failure by any of the claimed methods." (Action at pages 7-8). Applicants respectfully disagree.

The art has recognized the significance of the inventors' achievement in identifying the S16E mutant phospholamban molecule that is presently claimed, as demonstrated in the enclosed references. In Crystal, *Gene Therapy*, 10:2-3 (2003), the author (an editor of the journal) noted that "[n]umerous studies have shown the gene therapy can transiently forestall heart failure. Now, for the first time, Chien and his colleages have demonstrated that experimental heart failure can persistently be prevented with gene therapy." (Id., at 2). Citing to the inventors' paper in Hoshijima, et al., *Nat.Med.*, 8:864-871 (2002), Crystal notes that:

> "[w]ith an adeno-associated virus vector, Chien and his co-workers were able to persistently express S16E phopholamban in the heart. they also showed that S16E phospholamban gene therapy, despite not addressing the primary cardiac abnormality in the BIO14.6 hamsters [as a cure], enhanced a variety of parameters associated with cardiac function. The achievement of Chien and his colleagues is significant in two ways. First, while heart failure can wax and wane, it is a chronic condition requiring persistent therapy. The new study is the first to demonstrate that gene therapy can achieve this. **Second, this study shows that enhancement of SERCA function can be used to treat heart failure caused by other defects.**" (Id. at 3; emphasis added).

In accord, see Zhao, et al., *Hell.J.Cardiol.*, 45:208-217 (2004): the inventors' work showed "chronic inhibition of PLN [phospholamban] by delivering a pseudophosphorylated S16E-PLN into the heart [to] successfully prevented progressive heart favilure in inhereited cardiomyopathic hamsters, and also rescued the cardiac dysfunction and remodeling induced by myocardial infarction, in a model of acquired heart failure." (Id., at 214). As predicted in the Specification, S16E has activity comparable to that reported herein for the K3E/R14E molecule (see, e.g., Specification at page 22, lines 5-25).

Therefore, Applicants respectfully submit that the Specification clearly and sufficiently teaches how to make and use both the S16E and K3E/R14E mutant molecules, each of which possesses the ability to suppress phospholamban activity, thereby increasing SERCA2 activity with the therapeutic implications for heart failure as described. Reconsideration and withdrawal of the enablement rejection is therefore warranted and requested.

CONCLUSION

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-0872. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-0872.

If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 50-0872.

Respectfully submitted,

Date 9-1-2004 By _____

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